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Personalised Predictions of Endovascular Aneurysm Repair Success Rates: Validating the ERA Model with UK Vascular Institute Data

M. Barnes [a], M. Boult [b], M.M. Thompson [c], P.J. Holt [c], R.A. Fitridge [b,*]

[a] *CSIRO Mathematics, Informatics and Statistics, Glen Osmond, SA 5064, Australia*
[b] *Department of Surgery, University of Adelaide, The Queen Elizabeth Hospital, 28 Woodville Road, Woodville South, SA 5011, Australia*
[c] *St George's Vascular Institute, St James' Wing, St George's Hospital, London SW17, UK*

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Abstract *Objective:* The objective of this study was to externally validate the existing Australian Endovascular aneurysm repair Risk Assessment (ERA) Model using data from a major vascular centre in the United Kingdom.
Methods: Data collected from 312 endovascular abdominal aortic aneurysm repair patients at St George's Vascular Institute, London, UK were fitted to the ERA Model.
Results: Despite St George's patients being sicker ($p < 0.001$), having larger aneurysms ($p < 0.001$) and being more likely to die ($p < 0.05$) than the Australian patients, their data fitted the ERA Model well for the risk factors early death, aneurysm-related death, three-year survival and type I endoleaks as evidenced by higher area under ROC curves and/or higher R^2 goodness of fit statistics than the Australian data.
Conclusions: The first external validation of the ERA Model using data from St George's Vascular Institute suggests that this tool can be used in different countries and hospital settings. The authors believe the ERA Model is robust and allows valid personalised predictions of outcomes by surgeons treating routine aneurysms as well as those in tertiary referral practices with more adverse outcomes.

Introduction

The Endovascular aneurysm repair Risk Assessment (ERA) Model was developed in 2007 using data obtained from an Australian audit of endovascular aortic aneurysm repair (EVAR).[1] The audit followed the outcomes for 961 patients who underwent elective or semi-urgent repair between 1999 and 2001 for a minimum of five years. The ERA Model is

* Corresponding author. Tel.: +61 8 8222 7711; fax: +61 8 8222 6028.
E-mail address: evar.trial@adelaide.edu.au (R.A. Fitridge).

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available at the following website (www.health.adelaide.edu.au/surgery/evar); the user interface is shown in Fig. 1. Individual scenarios for patients are included in the 2008 paper by Barnes et al.[1]

The ERA Model enables clinicians to enter up to eight pre-operative variables for a patient, in order to derive the predicted likelihood of primary endpoints such as early death, aneurysm-related death, survival, type I endoleaks and mid-term re-interventions. Secondary endpoints include technical and clinical success, type II endoleaks, graft complications, migration, rupture and conversion to open repair.

Information pertaining to the Australian audit of EVAR has been published previously.[2,3] These articles describe the predictors of success following EVAR (ASA, age, aneurysm size, creatinine, neck angulation and infra-renal neck) that were found to best predict early and mid-tem outcomes and were therefore included in the ERA Model.

We described the development of the ERA Model in our 2008 paper.[1] Generalised linear regressions with the 'logit' link (logistic regressions) were used to determine which of the eight pre-operative variables should be included in the ERA Model for each endpoint. Survival analysis could have been used for some endpoints (e.g. aneurysm-related death and survival) as shown previously.[2] However endpoints such as conversion to open repair and early death are not amenable to survival methods. Hence, for reasons of simplicity logistic regression was the only method used for the ERA Model. Percentage estimates of three and five year survival are readily interpretable by surgeons and patients.

Some outcomes shown in the ERA Model have relatively wide confidence intervals (CIs). This is not surprising as these CIs are based on the range of outcomes for a similar group of patients in the original Australian audit. Hence, CIs provide additional information for surgeons and their patients into the possible variation that can occur and which may help them decide whether or not to proceed with the EVAR.

We previously described internally validating the ERA Model using bootstrapping.[1] Bootstrapping is a model validation technique which resamples from the data at hand.[4] Here we describe externally validating the model using data pertaining to 312 patients who underwent EVAR at St George's Vascular Institute, London, UK, between April 2001 and March 2007.

According to a recent systematic review by Chambers et al. the ERA model is currently the only risk modelling study to have developed risk algorithms '*from scratch*' and the review concluded that along with three other studies developed using existing risk algorithms it appears to be '*potentially the most useful for clinical decision-making*'.[5] Their review of risk modelling studies also reported a general lack of validated quality assessment tools. Hence, one purpose of this paper is to further demonstrate the validity of the ERA Model with external data.

Methods

De-identified data for 312 EVAR patients who underwent procedures between April 2001 and March 2007 at St George's Vascular Institute, London, UK, were provided in Excel spreadsheet format. The data were mapped and checked to ensure all required fields corresponded with those used in the ERA Model.

Pre-operative variables

The model determines the likely outcome following surgery based on five readily available pre-operative variables (age at operation in years), American Society of Anaesthesiologists

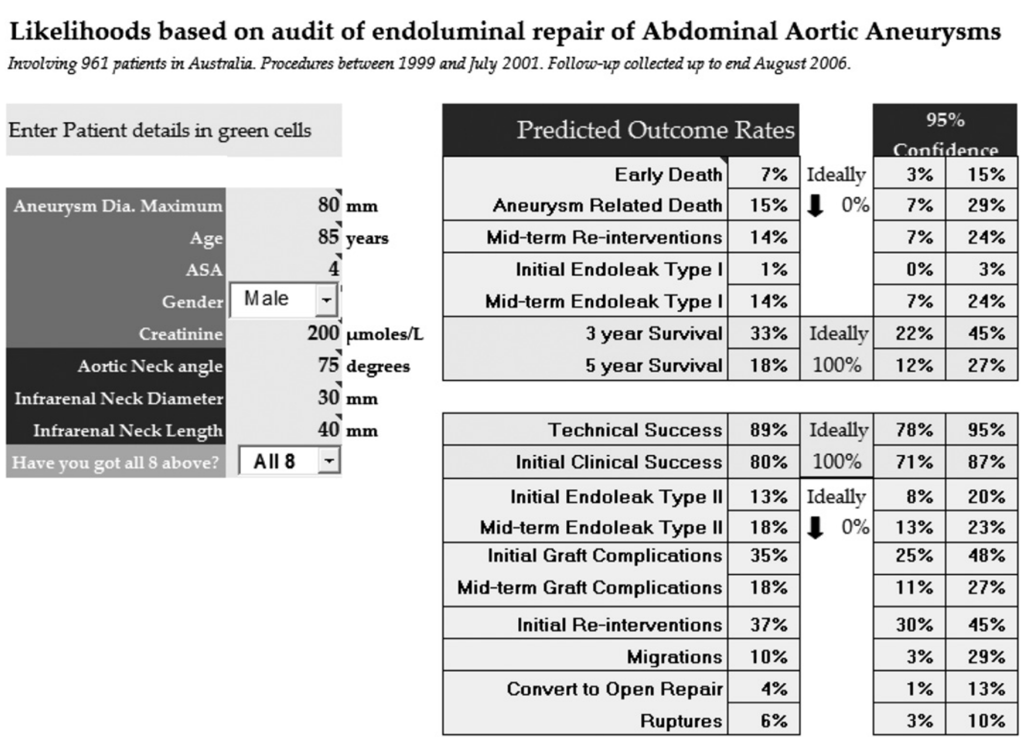

Figure 1 ERA Model user interface.

(ASA) rating (I—V), gender, aneurysm diameter (mm) and creatinine (μmol/L). The input of three additional post-imaging variables further helps to refine the results; aortic neck angle (degrees), infra-renal neck length (mm) and infra-renal neck diameter (mm).

The regions of applicability used for the ERA Model (i.e. the region within which most of the Australian data fell where the model is reliable) are as follows: age (55—90 years), ASA (I—IV), maximum aneurysm diameter (40—80 mm), creatinine (60—200 μmol/L), infra-renal neck length (6—45 mm), infra-renal neck diameter (17—32 mm). Where an individual's results exceed any of these values the nearest limit applies.

Table 1 shows which pre-operative variables were included in each of the outcome models. Blank cells denote non-inclusion. Cells listing *p*-values indicate inclusion. For example, aneurysm diameter, age, ASA, and creatinine were all used for the 3-year survival outcome model.

The inclusion criteria used was Akaike's Information Criterion (AIC). AIC estimates the goodness of fit of a model. The reduction in AIC compares the fit with and without each term included.[6] *p*-values are displayed because they are more readily understood than a reduction in AIC. They are likelihood ratio *p*-values.[1,7,8] Even though some *p*-values are greater than the traditional cut-off of 0.05, the reduction in AIC was significant, and therefore were included in the model.

All eight of the pre-operative variables used in the ERA Model had been collected at St George's.

Missing data for pre-operative variables were dealt with as follows. Two patients with missing pre-operative aneurysm diameter measurements were omitted. 18 missing ASA values were assumed to be the most common ASA of III (48% St George's EVAR patients had ASA III, Table 2). Postoperative infra-renal neck diameters and length were used where pre-operative was missing in two & three cases respectively. Hence, data for 310/312 patients were used.

Postoperative outcomes

Data for early death (i.e. death within 30 days of the original procedure) was readily available. Aneurysm-related deaths included early deaths, deaths within 30 days of an aneurysm-related procedure and deaths due to aneurysm rupture. Due to the recency of much of the St George's data, only around half could be used to assess 3-year survival ($n = 144$). Deaths were reported up to 18 May 2008; therefore only patients with procedures before 19 May 2005 were used to validate 3-year survival.

Data for type I & II endoleaks were assessed as follows: initial endoleaks were those documented from day 1 to day 30; mid-term endoleaks were those occurring after day 30.

Initial re-interventions were those performed on the same day or within 30 days of the EVAR procedure and mid-term interventions were those performed more than 30 days after the initial procedure.

Some outcome measures that were originally included from the Australian dataset could not be assessed for St George's data. The recency of the data meant that five-year survival data was not available; only 144/310 patients had sufficiently long follow up to be included in the 3-year survival analysis. There were too few migrations (7/310) and conversions to open repair (0) to assess the model. Graft complications, clinical and technical success were not available.

External validation

Predictions were made using the St George's data predictor variables and the Australian ERA Model coefficients. The goodness of fit of these models was assessed using Frank Harrell's Design package.[9] Specifically, the val.prob function was used to compare the predicted values for St George's data with the actual observed outcomes. The goodness of fit of St George's outcomes was assessed using the following statistics.

- The area under the receiver operating characteristic (ROC) curve,
- R^2, specifically Nagelkerke-Cox-Snell-Maddala-Magee R^2 statistic,

Predictions conducted in the S-plus package did not make use of the region of applicability adjustments. Predictions were made for the actual value of each predictor for each patient. For example when the maximum aneurysm diameter was very high, the actual diameter was used for predictions, rather than using the ninety-fifth percentile of the Australian data (top applicability limit). Eleven percent of UK data was higher than the upper limit of Australian region of applicability.

Table 1 Pre-operative variables used to develop each original outcome model (*p*-values).

Pre-operative variable Outcome	Aneurysm Diam.	Age	ASA	Gender	Creatinine	Aortic neck angle	infra-renal neck diam.	infra-renal neck length
3-Year survival	<0.001	<0.001	<0.001		0.002			
Aneurysm-related death	<0.001		0.030					
Early death	0.001	0.070						
Initial re-interventions			0.057					
Mid-term re-interventions				0.045	0.029	0.014		
Initial endoleak type I								0.007
Mid-term endoleak type I	0.005						0.130	
Initial endoleak type II			0.074	0.021				
Mid-term endoleak type II		0.110		0.088				

Table 2 Predictor variables: St George data compared to Australian data.

	St George's data	Australian data	*p*-Value
Male ratio	90%	86%	
Mean age	77.4 ± 7.8	75 ± 6.9 years	**<0.001**
ASA I	0%	3%	0.79
ASA II	24%	32%	**0.007**
ASA III	48%	59%	**<0.001**
ASA IV	27%	6%	**<0.001**
Mean aneurysm size[a]	64 mm	58 mm	**<0.001**
Aneurysms <55 mm	19%	44%	**<0.001**
Mean creatinine (μmol/L)	118	115	0.48
Creatinine <120 (normal)	70%	67%	
Mid (120–150)	18%	21%	
High (>160)	11%	12%	
Mean infra-renal neck length	23.7 mm	25.7 mm	**0.018**
≤20	54%	25%	**<0.001**
>20	46%	75%	**<0.001**
infra-renal neck diameter (mm)	23.7	23.6	0.70
Aortic neck angle ≥45°	30%	15.6%	**<0.001**

[a] Eleven percent of the St George's data for maximum aneurysm diameter was above the region of applicability limit of 80 mm used in the ERA Model.

Results

Comparison of St George's Vascular Institute and Australian data

Tables 2 and 3 provide a comparison of rates for data from St George's and the Australian audit. The following are worth noting. There were considerably more perioperative (early) deaths in the St George's data, 4.2% as compared to 1.8% Australian perioperative deaths ($p = 0.003$). There were considerably more aneurysm-related deaths in the St George's data, 4.8% as compared to 2.6% Australian deaths ($p = 0.03$). St George's patients were less likely to survive 3 years than Australians; 69% compared to 81% ($p < 0.001$). St George's patients more often required initial interventions; 41% compared to 32% ($p < 0.001$). Fewer of the EVAR procedures at St George's were performed on small aneurysms (<55 mm); 19% compared with 44% ($p < 0.001$) and conversely. EVAR procedures at St George's were performed on larger aneurysms; UK average 64 mm compared with 58 mm in Australia ($p < 0.001$). Sicker patients, as evidenced by an ASA rating of IV had the EVAR procedure at St George's (27%) compared with 6% in Australia (6%) ($p < 0.001$). Aortic neck angles in the St George's data were more often ≥45 degrees; 30% compared with 15.6% ($p < 0.001$). St George's neck lengths were generally shorter; 54% ≤ 20 mm compared to 25% ($p < 0.001$).

Goodness of fit

Some of the assessments of goodness of fit are shown in Table 4. The table compares the fit of the St George's data with the Australian models. Generally there was not a large difference in fit between the St George's and Australian data as shown by the small differences in areas under the ROC curves in Fig. 2.

St George's patients as a whole were sicker ($p < 0.001$), had larger aneurysms ($p < 0.001$), more difficult anatomy

Table 3 Outcome rates: St George's data compared to Australian data.

	St George's data[a] % (*n*)	Australian data % (*n*)	*p*-Value
Perioperative (early) death	4.2% (13)	1.8% (17)	**0.003**
Aneurysm-related death	4.8% (15)	2.6% (25)	**0.03**
3-Year survival	69.4% (100/144)	80.7% (774/959)	**<0.001**
Endoleaks			
Initial Type-1	3.2% (10)	2.9% (28)	0.12
Initial Type-2	4.8% (15)	7.0% (67)	**0.05**
Mid-term Type-1	3.2% (10)	4% (36)	0.118
Mid-term Type-2	9.7% (30)	12% (111)	0.055
Initial interventions	41% (126)	32% (262)	**<0.001**
Mid-term interventions	11.3% (35)	11.6% (109)	0.07

Bolding indicates significance at the 0.05 level.

[a] St George's rates are usually out of 310 patients. Three-year survival only included 144 patients who had their EVARs more than 3 years before survival data collected.

Table 4 Goodness of fit for St George's Vascular Institute and Australian data.

	Early death	Aneurysm-related death	mid-term interv.	Initial endoleak type I	mid-term endoleak type I	Survival 3 year	Initial endoleak type II	mid-term endoleak type II	Initial interv.
St George's Vascular Institute									
c ROC	**0.80**	**0.83**	0.51	0.57	**0.73**	0.70	0.53	0.49	0.52
R^2	**0.111**	**0.132**	0.003	0.001	**0.061**	**0.132**	0.002	0.000	0.002
Australian data									
c ROC	0.71	0.75	0.60	0.64	0.64	0.71	0.59	0.54	0.54
R^2	0.075	0.110	0.029	0.049	0.049	0.128	0.030	0.009	0.005

Interv = intervention.
Where: c ROC is the Area under ROC curve. A ROC value approaching 1 suggests a better model than those close to 0.5.
R^2 index.
The higher the R^2 the better the model fit.
Bolding indicates higher goodness of fit values for St George's data than the Australian data.

(shorter and more angulated necks, $p < 0.001$), and were more likely to die ($p < 0.05$) than the Australian patients. However, the ERA Model provided a comparable fit for the St George's patient outcomes of early death, aneurysm-related death, 3-year survival and mid-term type I endoleaks than for the Australian data as evidenced by higher area under ROC curves and/or higher R^2 goodness of fit statistics (shown by bolding in Table 4).

That the ERA Model performed well on predictions of perioperative and aneurysm-related death and 3-year survival is highly relevant as these are clearly important endpoints. The models estimating the likelihood of requiring an additional intervention or having type II endoleaks did not perform as well, with low ROC area and low R^2, indicating room for improvement for these two outcomes.

Discussion

The ERA Model is simple for surgeons and patients to use as it only requires 8 pre-operative variables to be entered. We believe that by keeping the model simple its accessibility is increased. For the ERA Model to be useful it was necessary to validate it with external data. We have presented here the results of validating the model with data supplied from a leading specialist vascular centre in the UK, the St George's Vascular Institute. Previously the model had been internally validated, and could only be used confidently within the Australian context. Whilst further ongoing validation is planned, it is pleasing that the new data presented a good fit, on a number of important outcomes. Three-year survival achieved a very comparable fit to the Australian data, even though only half the cohort was available. The similar R^2 and ROCs indicate it is likely that this goodness of fit will remain as more data is gathered.

As seen in Table 2, there are significant differences between the population of patients who undergo EVAR in Australia and those who do so at St George's. The results show that sicker patients with larger aneurysms and more difficult anatomy are managed at St George's Vascular Institute. This may partly reflect the tertiary referral nature of this Institute's practice. The model allows personalised predictions for these disparate data sets and validates the higher incidence of adverse outcomes in the St George's data set. Such an approach allows valid predictions of outcomes in units by surgeons treating routine aneurysms and those in tertiary referral practices who would be expected to have more adverse outcomes due to treating more complex aortic aneurysms.

Despite the differences between the two populations the ERA Model fit for early death, aneurysm-related death, 3-year survival and mid-term type I endoleaks for St George's patients was comparable to that of Australian patients. This suggests that the ERA Model is robust, in the sense that it has been validated for a different population of patients in the UK and appears to be relevant beyond the region of applicability of the Australian data for the key outcomes of early death, aneurysm-related death, 3-year survival and mid-term type I endoleaks.

Not all outcomes were available in the St George's data. Outcomes that were tested but performed less well were initial type I endoleaks, type II endoleaks and re-interventions. Interestingly, apart from initial type-1 endoleaks, these outcomes were not as strong a fit in terms of area under the ROC curve or R^2 as the other outcomes for the Australian data, and in each case less so for the UK data. Whilst type II endoleaks are not as clinically important as those pertaining to survival, the need to undergo

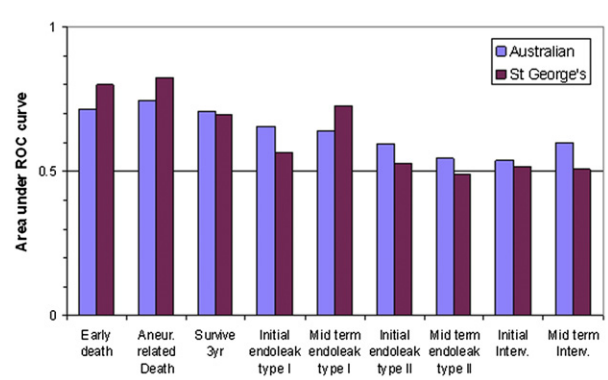

Figure 2 Area under ROC curve for nine outcomes: St George's and Australian fit. A ROC value approaching 1 suggests a better model than those close to 0.5.

subsequent procedures for an abdominal aortic aneurysm, especially in the perioperative period, is clearly a major consideration for a patient and associated with significant complications.

The data on which the ERA Model is based (and tested here) may have some bearing on type I endoleaks as the procedures used older graft technology. The advent of newer endografts may influence the technical success of endografting and potentially impact on outcomes and incidence of endoleaks. Hence, type I endoleaks and early re-interventions will need to come under close scrutiny as part of our new study into graft outcomes as they are likely to be subject to model drift.

Some outcomes performed poorly indicating room for improvement. Additional interventions and type II endoleaks had low ROC area and low R^2. During the next five years substantial work will be put into testing and improving the model based on new data from Australia and the UK. Survival techniques and more complex relationships may be included. Predictor variables other than the eight used currently may significantly improve the ability to predict these outcomes.

The aim of developing the ERA Model was to provide a useful tool for surgeons and patients to help with decision-making and risk assessment. Even though EVARs are now performed routinely, they are not always the best alternative for an individual patient. If the risk of graft complications is high then it may be more appropriate to perform an open aneurysm repair (or possibly fenestrated repair). The model will also help quantify perioperative mortality and mid-term survival in individuals with significant co-morbidities who may be most appropriately managed without intervention.

Generalised statistical outcomes are not always helpful when making individual decisions, and although clinical experience is paramount, being able to back this up with a robust model is helpful. Validating the model internally and now externally are the first steps towards ensuring the model is robust. Our aim over the next five years is to test the model with new Australian data ($>$1000 patients) and other large external datasets to see if it can be improved and to determine whether new and upgraded stent-grafts have had an impact on patient outcomes. We also aim to continue testing and developing the model using external data during this time to assess how well the ERA Model behaves with data from different populations.

Conflict of Interest

None.

Acknowledgements

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